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CONTENTS

19-001

Association of Dose Reduction of Abiraterone Acetate plus Prednisone or Enzalutamide and PSA Progression in Veterans with Metastatic Castration Resistant Prostate Cancer

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Background: Rising PSA levels in men with metastatic castration-resistant prostate cancer (mCRPC) may indicate disease recurrence or progression. Clinical trials have shown that abiraterone acetate plus prednisone (AAP) and enzalutamide (ENZ) improved PSA response, delayed time to PSA progression, and prolonged overall survival in men with mCRPC. However, dose reduction or treatment interruption may be necessary in case of side effects, toxicity, or drug-drug interactions. This study aims to evaluate the association between dose reduction and PSA progression in patients with mCRPC.

Methods: Veterans Health Administration electronic health record data were used to conduct a retrospective longitudinal study in Veterans who initiated AAP or ENZ (index) between April 2010 and December 2016, had ≥12 months of enrollment before treatment initiation (baseline), were diagnosed with PC, and had at least two PSA measurements post-index, the first of which was within 3 months post-index. PSA progression was defined as the first rise in PSA that was ≥2 ng/mL and at least 25% above the nadir (defined as the lowest PSA measurement observed post-index). Patients were followed until the earliest of treatment discontinuation, loss to follow-up, death, or end of data availability. The relative dose intensity (RDI), which was calculated as the ratio of the dispensed dose (total dispensed dose over last two months) to the standard dose recommended in the prescribing information, was used to evaluate dose reduction and was updated monthly. A Cox proportional hazards model adjusting for baseline characteristics was used to evaluate the association between PSA progression and RDI<80%.

Results: A total of 6,069 Veteran men formed the study population. Mean (SD) age was 74.7 (9.2) years and the majority were white (69.5%). Mean (SD) follow-up was 12.3 (8.5) months. During follow-up, PSA progression occurred in 62.7% of patients. Of AAP and ENZ patients, respectively 63.6% and 67.2% had at least one occurrence of RDI <80%. The Cox model showed that an RDI<80% was associated with an 8.8% increase in the likelihood of having PSA progression (hazard ratio: 1.087, P=0.019). Similar findings were found when index treatments were assessed in separate models.

Conclusion: In this study of Veteran men with mCRPC treated with AAP or ENZ, dose reduction was associated with an increased hazard of experiencing PSA progression regardless of which agent they were treated with.

Source of Funding: This research was funded by Janssen Scientific Affairs, LLC.

19-002

The Ratio of the Number of Biopsy Specimens to Prostate Volume (Biopsy Density) > 1.5 Improves the Detection of Clinically Significant Cancers in men Undergoing Transperineal Biopsy of the Prostate

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Objective: Template-guided transperineal mapping biopsy (TPMB) removes a larger number of biopsy cores when taken at each 5 mm intervals. We investigated the number of biopsy cores required at TPMB to optimize the detection of prostate cancer and clinically significant disease (csPCA)

Methods: 436 men underwent TPMB in the OR where biopsies were taken through a perineal grid at 5mm intervals. Sagittal lengths longer than 20 mm were biopsied in-line. The thoroughness of the TPMB was physician dependent. Prostate volume (PV) was determined at the time of TPMB. Each biopsy core was individually processed and the "biopsy density (BD)" was calculated by dividing the total number of cores retrieved by the PV. Associations between cancer diagnosis and csPCa with PSA, PSAD and BD was tested by ANOVA with bootstrap, and chi-square tests. Regression analysis was used to determine which factors were associated with a +TPMB and GS7 or higher.

Results: The mean age, PSA number of cores, positive cores (PC) and BD were 65 years, 59.4 (range 16-151), 6.5 (range 1-37) and 1.46 (range 0.39-3.67). 299/436 (68.6%) had a +TPMB. The mean BD for a +TMPB was 1.61 vs. 1.14 for a negative one ($p<0.001$). +TPMB versus -TPBM for PSA < 10 and > 10 ng/ml were associated with a BD of 1.62 vs. 1.16 ($p<0.001$) and 1.52 vs. 1.02 ($p=0.002$), respectively. BD cut points of < 0.5, >0.5-1.0, >1.0-1.5 and >1.5 were associated with a +TPMB in 25%, 37.4%, 70.7% and 84.9% ($p<0.001$). Dichotomizing BD to < 1.5 vs > 1.5 demonstrated a +TPMB of 56.4% vs. 84.9% (OR 1.5, 95%CI 1.3-1.7, $p<0.001$). There was no difference in the number of +cores based on BD. GS6 was diagnosed slightly more with a greater BD: 61.6 vs. 50.4% ($p=0.073$). However, the number of +cores was greater in the men with higher BD: 4.9 vs. 3.6 ($p=0.036$) suggesting that a BD> 1.5 is better at diagnosing high volume GS6 disease. Regression analysis for +TPMB demonstrated as significant PSA ($p<0.001$), PSAD ($p<0.001$) and BD ($p<0.001$) and for GS7+ disease age ($p=0.005$) and PSA ($p=0.053$) and BD ($p=0.012$).

Conclusions: A biopsy density of at least 1.5 specimens per cc. of PV increases the diagnosis of prostate cancer by 1.5 times. A higher BD finds more csGS disease and while it also finds more GS6 cancers, these are at higher volume and may not be good candidates for active surveillance. A BD ≥ 1.5 should be considered the standard when performing TPMB to maximize prostate cancer diagnosis and the detection of clinically significant disease

19-003

Late Administration of Luteinizing Hormone-Releasing Hormone Agonists and Testosterone Levels >50 ng/dL in Prostate Cancer

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Introduction/Background: The importance of achieving and maintaining effective testosterone (T) suppression is well recognized in the treatment of advanced prostate cancer (PCa). The administration of luteinizing hormone-releasing hormone (LHRH) agonists is the preferred means of achieving this suppression. Increasing evidence suggests maintaining very low T levels to <20 ng/dL with ADT correlates with improved disease-specific survival in patients with advanced PCa. Consistent drug delivery with long-acting leuprolide acetate formulations is important in providing continuous T suppression throughout the course of treatment without T rising above castrate level (T breakthrough). However, T levels may rise significantly above castrate level, currently defined as >50 ng/dL, between administrations, especially if a subsequent dose is delayed. Contributing factors to late administrations are often operational and may include scheduling challenges and increasing number of advanced PCa patients requiring ADT. Compounding the effects of late administrations is the fact that although FDA approvals for ADT drugs are based on 28-day months, some insurers may mandate full calendar months (30 or 31 days) between doses for reimbursement purposes. This current study evaluated the timeliness of LHRH administrations and subsequent rate of T breakthroughs in patients with PCa.

Methods/Materials: A retrospective review of electronic medical records from 1/1/07-6/30/16 of 85,030 LHRH agonist administrations for PCa treatment was conducted to evaluate the percentage of late subsequent administrations and T tests with T>50 ng/dL. Late administrations were defined as those on or after day 33, 98, 129, 195 for 1, 3, 4, 6 month formulations, respectively. Descriptive statistics were used.

Results: For all LHRH agonist administrations, 26.9% of subsequent administrations were late: 14.4% were ≤1 week late, 3.1% were between 1-2 weeks late, and 9.4% were >2 weeks late. 28% of T values exceeded 50 ng/dL when administrations were late; in contrast, only 4% of T values exceeded this level when doses were administered early or on time.

Conclusions: After initiation of LHRH agonists, greater than a quarter of subsequent administrations were defined as late. Among late administrations, about half were >1 week late and more than a third were >2 weeks late. When LHRH agonist administrations were late, the proportion of T tests with T>50 ng/dL was increased as compared to early/on-time administrations. Late administrations were correlated with ineffective castration over 28% of the time. Considering the presumed clinical benefits of maintaining effective T suppression throughout a course of ADT, clinicians should administer treatments within approved dosing instructions, routinely monitor T levels, and consider prescribing treatments with proven efficacy through the dosing interval to maintain T at castrate levels.

Conflict of Interest and Disclosure Statement: Study was funded by Tolmar Pharmaceuticals, Inc.

19-004

Biopsy-Derived Cell Cycle Progression Score Outperforms Pathologic Upgrading or Upstaging in Predicting Biochemical Recurrence After Surgery

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Introduction: Improved prognostic markers for prostate cancer are an important part of addressing the over- and under-treatment of prostate cancer. Active surveillance (AS) has gained rapid adoption for men with low-risk disease but concern about pathologic upgrading or upstaging is considered a significant risk factor for progression, and therefore, has in some cases limited clinical adoption of AS. Prolaris measures the expression level of cell cycle progression genes and has demonstrated accurate prediction of prostate cancer aggressiveness in numerous clinical settings. In this study, we compare biopsy-derived Prolaris to radical prostatectomy (RP) derived adverse pathology (upgrading or upstaging) in predicting biochemical recurrence (BCR) after surgery.

Methods: CCP testing was performed on the biopsy specimens from pooled cohort of men treated by RP for low risk localized prostate cancer, and the score was combined with CAPRA using a validated algorithm to generate a CCP clinical risk (CCR) score. Adverse pathology was defined as patients with biopsy Gleason score ≤ 3+4 and clinical stage ≤ T2 who had a post-RP Gleason score ≥ 4+3 and/or a post-RP pathological stage ≥ T3. Association with BCR was evaluated by Cox proportional hazards model.

Results: In the pooled cohort of 557 men, there were 56 (10%) men with adverse pathology and 116 (20%) with BCR. In multivariable analysis, CCP was strongly associated with BCR ($p = 1.7 \times 10\text{-}3$, $\chi^2 = 9.87$). Both CAPRA and adverse pathology were also significant, but contributed substantially less prognostic information to the final model ($p= 0.013$, $\chi^2 = 6.18$ and $p= 0.041$, $\chi^2 = 4.16$, respectively). The CCR score provided the most prognostic information for predicting BCR in univariate data.

Conclusions: These data indicate that a patient's biopsy-derived CCP score may contain more robust predictive information for eventual BCR than adverse pathology after RP. Further, these data can be used to provide significant risk discrimination to patients who are considering AS.

19-005

Patient Valuation of Castration-Resistant Prostate Cancer Health States

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IIntroduction and Objective: More than 84% of patients initially diagnosed with castration-resistant prostate cancer (CRPC) are metastatic. Of patients who are diagnosed with non-metastatic CRPC (nmCRPC), 33% develop metastases within two years. There is paucity of research describing patient-reported outcomes in nmCPRC. The objective of this study was to evaluate the relative preferences of CRPC patients for metastatic versus non-metastatic heath states.

Methods: Men in the US with nmCRPC or mCRPC participated in a cross-sectional, vignette-based, online time trade-off (TTO) web-based survey study. Study participants were recruited by a patient panel company via urologist/ oncologist referrals. The following three health states were drafted and refined through a literature review, clinician interviews, and pilot interviews with CRPC patients: (1) living with nmCRPC (2) mCRPC before chemotherapy, and (3) mCRPC either on or after chemotherapy. In a web-based survey, patients were provided vignettes describing these health states, and were then presented with a series of choices between spending 5 years in a given health state versus spending varying amounts of time in full health (in 3-month trading increments). Full health meant no health problems of any kind and usual activities could be performed without difficulty. Responses to these TTO choice tasks were used to estimate utilities for the three health states, with higher utility scores indicative of greater patient preference.

Results: Ninety-six participants completed the TTO choice tasks (mean age ± SD = 64.2 ± 14). High cholesterol (n=45, 47%) and hypertension (n=36, 38%) were the most common co-morbidities. Mean utilities were 0.80 (SD=0.36) for nmCRPC, 0.74 (SD=0.43) for mCRPC before chemotherapy, and 0.64 (SD=0.47) for mCRPC either on or after chemotherapy. The utility score for the mCRPC on or after chemotherapy health state was statistically significantly lower than that for nmCRPC ($p < 0.01$).

Conclusions: The nmCRPC health state utility score was significantly higher compared to the more severe mCRPC health state. Findings indicate the significant value that men with CRPC place on avoiding the development of metastases and treatment with chemotherapy. With new treatments indicated for nmCRPC patients currently in clinical development, the study can provide a useful reference for evaluating such interventions.

Source of Funding: Janssen Scientific Affairs, LLC

Value of Care: Cost and Outcomes Measures

19-006

Matching-Adjusted Indirect Comparison of the Efficacy of Apalutamide and Enzalutamide in the Treatment of Non-Metastatic Castration-Resistant Prostate Cancer

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OBJECTIVES: Apalutamide is a next-generation androgen receptor inhibitor; FDA approved for the treatment of nonmetastatic castrate-resistant prostate cancer (nmCRPC). Both apalutamide (SPARTAN) and enzalutamide (PROSPER) have been studied in placebo-controlled trials. In the absence of comparative trials between these compounds, the agents were indirectly compared on metastasis-free survival (MFS) and overall survival (OS).

METHODS: Individual patient-level data from SPARTAN and published data from PROSPER were utilized. An anchored matching-adjusted indirect comparison (MAIC) was conducted by weighting the patients from the SPARTAN trial to match baseline characteristics (i.e., age, Gleason Score, Eastern Cooperative Oncology Group Performance Status, serum prostate specific antigen [PSA], PSA doubling time [PSADT], use of bone targeting agents, and surgical prostate cancer procedures) reported for PROSPER. Hazard ratios (HR) for MFS (defined as in PROSPER as the time to radiographic progression or death within 112 days of treatment discontinuation), and OS were re-estimated for SPARTAN using weighted Cox proportional hazards models and indirectly compared to MFS, and interim OS of PROSPER using a Bayesian network meta-analysis.

RESULTS: From the SPARTAN population (N = 1,207), a total of 1,171 patients were balanced to the PROSPER population (N = 1,401) by the matching process. MAIC-based SPARTAN HRs (95% confidence interval) for apalutamide vs placebo + androgen deprivation therapy were significant at 0.27 (0.21, 0.34) for MFS and 0.62 (0.41, 0.94) for OS. MAIC-based HRs (95% credible interval) for apalutamide vs enzalutamide were 0.92 (0.69, 1.24) for MFS and 0.77 (0.46, 1.30) for OS. The Bayesian probabilities of apalutamide being more effective than enzalutamide were 70.1% for MFS, and 83.3% for OS.

CONCLUSIONS: Based on available RCT-data from SPARTAN and PROSPER and Bayesian probabilities, MAIC-results suggest that nmCRPC patients treated with apalutamide benefited from a more favorable MFS and OS compared to enzalutamide. These results will be confirmed further with more mature data.

19-007

Cardiometabolic Effects Associated with Androgen Deprivation Therapy: Potential Mechanisms of Action

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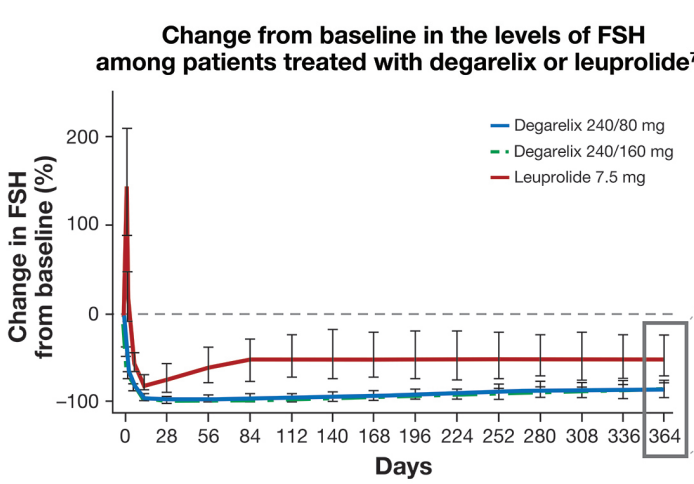
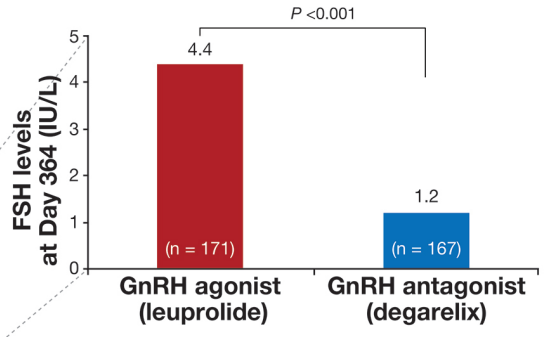
BACKGROUND

- Androgen deprivation therapy (ADT) may be associated with increased cardiovascular (CV) morbidity and mortality in patients with advanced prostate cancer[1-4]
- Although gonadotropin-releasing hormone (GnRH) receptor agonists and antagonists both reduce testosterone to castrate levels, recent studies suggest that there may be differences in CV risk between GnRH receptor agonists and antagonists[5,6]
  - A meta-analysis of six phase 3 studies reported a significantly lower risk of cardiac events in men with preexisting CV disease within 1 year of initiating treatment with a GnRH receptor antagonist compared with treatment with a GnRH receptor agonist (hazard ratio = 0.44; $P = 0.002$)[5]
  - A separate meta-analysis of results from five phase 3 studies found that treatment with the GnRH receptor antagonist degarelix was associated with a lower incidence of severe CV side effects compared with

GnRH antagonists decrease FSH more than GnRH agonists: potential differences in ca

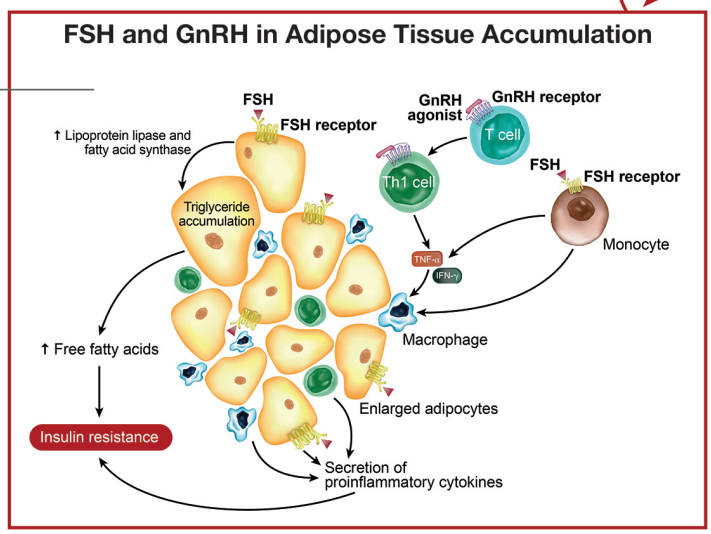


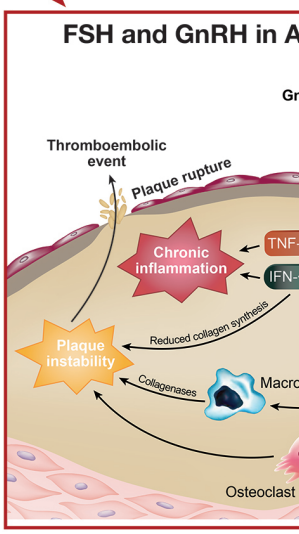


FSH levels

Increased inflammation → Inflammatory mediators → Less inflam comp

- FSH stimulation promotes lipid accumulation in adipose tissue in a concentration-dependent manner[13]
  - Altered adipose tissue further contributes to inflammation through the overexpression of TNF-α and IL-6[14-16]
  - FSH levels have been shown to positively correlate with body mass index[13]
- Increased secretion of free fatty acids and pro-inflammatory cytokines leads to insulin resistance; this altered insulin action contributes to hypertriglyceridemia and non-alcoholic fatty liver disease[17-20]





treatment with GnRH receptor agonists (1.6% vs 3.6%; odds ratio = 0.55; *P* = not significant)[6]

- Differences in the mechanism of action between GnRH antagonists and agonists may be responsible for the different cardiometabolic profiles associated with forms of ADT
- Data from a clinical trial demonstrated that degarelix more effectively suppressed serum levels of follicle-stimulating hormone (FSH) compared with the GnRH receptor agonist leuprolide[7]
- FSH is thought to promote the development of inflammation, adiposity, insulin resistance, and atherosclerosis[8]; therefore, we sought to develop a model that would help us better understand how FSH contributes to the cardiometabolic morbidity observed with ADT

OBJECTIVE

- To develop a model explaining the mechanisms mediated by FSH that contribute to the cardiometabolic effects observed during ADT with GnRH receptor agonists and antagonists

METHODS

- A colloquium of experts in the treatment of prostate cancer was convened in May 2015 to discuss the current knowledge of FSH and its potential relationship with the undesirable cardiometabolic effects associated with ADT
- An in-depth review of preclinical and clinical literature in Medline and PubMed was conducted on specific topics of interest; this poster describes findings relevant to the mechanisms by which FSH may mediate the cardiometabolic effects of ADT

CONCLUSIONS

- Emerging evidence suggests that proinflammatory markers can be potentially driven by FSH and may contribute to differing cardiometabolic effects in ADT
- FSH levels were more suppressed with a GnRH receptor antagonist versus agonist[7]
- The model hypothesizes the importance of FSH as a biomarker when treating patients at risk for adverse cardiometabolic events with ADT
- Further insights into the mechanisms underlying the cardiometabolic events resulting from ADT are being investigated

ACKNOWLEDGMENTS

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*Figure reproduced from Klotz L, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int*. 2008;102(11):1531-1538, with permission from John Wiley and Sons.

rdiometabolic effects associated with ADT.

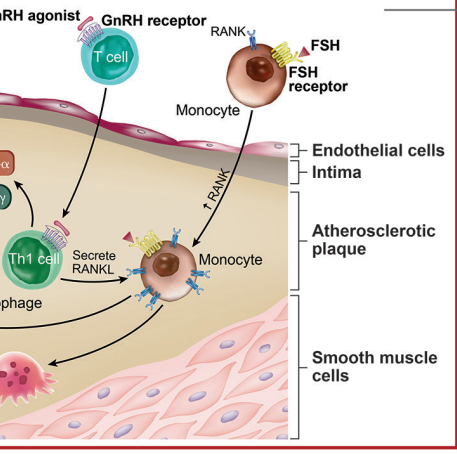
nadequate FSH control during ADT may contribute to profound metabolic differences between GnRH receptor agonists and antagonists, resulting in cardiometabolic morbidity

FSH has been shown to stimulate secretion of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)[9,10]

T-cell activation by GnRH receptor agonists induces a shift toward the type 1 T helper (Th1) phenotype associated with proinflammatory states[11,12]

nmation and risk of CV events ared with GnRH agonist

therosclerosis/Plaque Instability



- Heightened release of proinflammatory cytokines is linked to increased CV risk through promotion of atherosclerosis and plaque instability[14,21]

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19-008

Genomic Profiling of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) for the Evaluation of Rucaparib: Next-Generation Sequencing (NGS) of Tumor Tissue and Cell-Free DNA (cfDNA)

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Introduction & Objectives: The phase 2 TRITON2 (NCT02952534) and phase 3 TRITON3 (NCT02975934) studies are evaluating the poly(ADP-ribose) polymerase inhibitor rucaparib in patients with mCRPC who have a deleterious germline or somatic mutation in *BRCA1*, *BRCA2*, *ATM*, or other DNA damage repair (DDR) gene. Here we present interim results of central genomic screening of tissue samples and plasma cfDNA in TRITON2 and TRITON3.

Materials & Methods: Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples were profiled for genomic alterations in 395 genes, and plasma samples were profiled for genomic alterations in 70 genes, using Foundation Medicine, Inc., NGS assays.

Results: As of July 2, 2018, 1311 tumor tissue blocks (73%) and slides (27%) from primary prostate cancer tumors (84%) and metastases (16%) of 1214 patients with mCRPC were processed. The median sample age was 2.8 years (range, 4 days to 21 years). The NGS tissue test failure rate was 32%, mainly (18%) due to insufficient tumor content or DNA. In total, samples from 872 patients were sequenced successfully. Deleterious genomic alterations in *BRCA1*, *BRCA2*, and/or *ATM* were observed in 15% of patients with successfully sequenced samples: *BRCA1* (2%), *BRCA2* (7%), and *ATM* (6%).

In parallel, a total of 638 plasma samples from 606 patients with mCRPC progressing on prior therapy were sequenced. The median sample age was 2 days (range, 1–10 days). NGS was successful for 97% of the plasma samples, and in 93% of those, a genomic alteration was detected in at least 1 assayed gene. Deleterious genomic alterations in *BRCA1*, *BRCA2*, and/or *ATM* were observed in 19% of patients with successfully sequenced samples: *BRCA1* (2%), *BRCA2* (9%), and *ATM* (12%).

Conclusion: Genomic profiling of both FFPE tumor tissue samples and cfDNA using NGS successfully identified patients with a genomic alteration in a DDR gene for the evaluation of rucaparib in mCRPC. Additional genomic analyses will be presented.

19-009

Phase 3 HERO Study Design: Evaluation of the Safety and Efficacy of Relugolix, a Novel Oral GnRH Receptor Antagonist, in Men with Advanced Prostate Cancer

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Introduction: Relugolix is an oral, once daily, potent and selective non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist in development for the treatment of men with advanced prostate cancer. Unlike injectable GnRH agonists, oral relugolix lowers testosterone within 2 days by inhibiting pituitary release of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The ongoing HERO study is a phase 3 multinational, randomized, open-label, parallel-group study designed to evaluate the safety and efficacy of relugolix and leuprolide acetate for 48 weeks in men with androgen-sensitive advanced prostate cancer who require at least one year of continuous androgen deprivation therapy (ADT). This single Phase 3 trial is designed to achieve approval in the United States (US), Canada, European Union (EU), Japan and China.

Study Population: Approximately 1100 men with advanced prostate cancer who are not surgical candidates will be enrolled from ~200 sites globally. Eligible patients are randomized 2:1 to receive either relugolix 120 mg orally once daily for 48 weeks following a single oral loading dose of 360 mg on Day 1, or leuprolide acetate 3-month depot injection for 48 weeks. Randomization is stratified by geographic region, presence of metastatic disease, and age. Eligible patients must have evidence of biochemical relapse (rising prostate-specific antigen [PSA]) following local primary intervention with curative intent, newly diagnosed metastatic disease, and/or advanced localized disease, each with baseline serum testosterone ≥ 150 ng/dL. Patients may receive radiotherapy, cryotherapy, or high frequency ultrasound no sooner than 2 months after initiation of ADT. Patients may not have previously received ADT for greater than 18 months, or otherwise discontinued ADT at least 3 months prior to the baseline visit.

Study Endpoints: The primary analyses of efficacy and safety will be conducted after the first 915 patients (non-metastatic and metastatic) have completed study treatment. The primary endpoint of sustained testosterone suppression to castrate levels (≤ 50 ng/dL [1.7 nmol/L]) for 48 weeks while on study treatment will be assessed based upon 2 different criteria. For US approval, the relugolix arm must demonstrate a 48-week castration rate with the lower bound of the 95% confidence interval of at least 90%. For approvals in the EU, Japan and China, the primary endpoint is to demonstrate relugolix to be non-inferior to leuprolide in the proportion of men achieving sustained suppression of testosterone through 48 weeks as assessed by a noninferiority margin of 10%. Secondary endpoints include the time course and change in serum PSA, testosterone during relugolix treatment, testosterone recovery following discontinuation of relugolix, PSA progression, FSH suppression, quality of life, safety, pharmacokinetics, and pharmacodynamics.

The HERO study continues to enroll an additional 120 men with metastatic disease to evaluate a key secondary endpoint, the risk of progression to castration-resistant disease during the 48-week study period. Top-line results from the HERO study are expected to be announced in 2019.

Clinical trial information: NCT03085095.

19-010

Impact of Positron Emission Tomography with 18F-Fluciclovine on Management of Patients in the United States with Biochemically Recurrent Prostate Cancer: Results from the LOCATE Trial

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Background: Early and accurate localization of disease recurrence, when tumors are small and most amenable to localized therapy, may inform clinicians' management plans regarding localized salvage versus systemic therapy. 18F-Fluciclovine is approved for use with positron emission tomography/computed tomography (PET/CT) in Europe and the USA in patients with prostate-specific antigen (PSA) recurrent prostate cancer (PCa). At IPCU 2018, we presented the results of FALCON, a European multicenter clinical utility study. We now report results from LOCATE, a US prospective, multicenter study of the impact of 18F-fluciclovine on planned management recommendations for patients with recurrence of PCa after curative-intent primary therapy.

Methods : Men who had undergone curative-intent treatment of histologically confirmed PCa, but who were suspected to have recurrence based on rising PSA levels were enrolled prospectively. Each had negative or equivocal findings on standard-of-care imaging. 18F-Fluciclovine PET/CT was performed according to a standardized protocol. Treating physicians completed a questionnaire regarding the patient's management plan pre- and post-scan, recording changes to treatment modality (e.g., salvage radiotherapy to systemic androgen deprivation therapy) as 'major', and changes within a modality (e.g., modified radiotherapy fields) as 'other'.

Results: Between June 2016 and May 2017, 213 evaluable patients (median age = 67 years; median PSA = 1.00 ng/mL; median time from initial diagnosis = 54 months) were enrolled. 18F-Fluciclovine detected lesions in 122/213 (57%) patients. Of those, 52% were in in the prostate/bed and 66% % in extraprostatic regions (including lymph nodes, soft tissues and bone). The detection rate was broadly proportional to PSA levels at the time of scanning. Subject-level detection was shown to be 31% among those with the lowest PSA (0–0.5ng/mL) and 95% among patients with a PSA > 10 ng/mL

Overall, 126/213 patients (59%) had a change in management post-scan; 98/126 (78%) of these were 'major' and 88/126 (70%) were informed by positive PET/CT findings. The most frequent major changes were from salvage or non-curative systemic therapy to watchful waiting (32/126, 25%), from non-curative systemic therapy to salvage therapy (30/126, 24%) and from salvage therapy to non-curative systemic therapy (11/126, 9%).

Conclusions: In patients with PSA recurrent PCa and negative/equivocal standard imaging, 18F-fluciclovine PET/CT revealed one or more sites of disease recurrence in a majority of men, and frequently resulted in a change in management post-scan. Over three-quarters of all management changes were considered major. These results from a US prospective study suggest that 18F-fluciclovine PET/CT has the potential to improve management, but further investigation of the impact of such management changes on patient outcomes is warranted.

Conflicts of interest and funding: This study was sponsored by Blue Earth Diagnostics, Ltd. MQ is an employee of Blue Earth Diagnostics.

19-011

Men with PIRADS Score ≤ 3 and SelectMDx Score ≤ 30% can be Spared from Prostate Biopsy

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Introduction and Objective: The Prostate Imaging Reporting and Data System (PIRADS v2) score indicates risk of clinically significant (CS) prostate cancer (PCa) on multiparametric MRI (mpMRI). Men with PIRADS Score (PS) ≥ 3 are recommended for prostate biopsy, but PS ≤ 2 cannot rule out CS PCa. PCa biomarker tests can identify men with CS PCa prior to biopsy. We evaluated combined utility PS and biomarkers to identify CS PCa using 5 mm grid interval transperineal mapping biopsy (TMB) shown to have 98% correlation with radical prostatectomy pathology.

Methods: 39 patients had phi (prostate health index), SelectMDx, and mpMRI tests done prior to TMB after inconclusive TRUS biopsy results. mpMRI was reviewed by a radiologist and given PS of 3, 4, or 5 to designate intermediate, high, and very high risk of CS PCa defined as a lesion with high-grade (HG) PCa (Gleason Score ≥ 7) or volume ≥ 0.5 cc. phi was evaluated using proPSA, free PSA and total PSA in serum. SelectMDx test measured mRNA levels of the HOXC6 and DLX1 in post-DRE urine. Phi < 27 indicates free of PCa and SelectMDx score = 0% correlates with free of HG PCa. TMB results were read by a genitourinary pathologist. Multivariate logistic regression analyses (MLRA) and receiver operating characteristic (ROC) curves were used to determine diagnostic accuracy of each modality. DeLong test was used to determine statistical significance of ROC curves.

Results: The median age was 65 years with mean PSA 6.4 ± 5.9 ng/mL, PSA density (PSAD=PSA/gland volume) 0.16 ± 0.18, and phi 46.5 ± 22.9 at TMB. MB identified 34/39 (87%) patients with PCa and 15/34 (44%) had HG and 18/34 (53%) had CS PCa. Performance results are summarized in the Table. Area under curve (AUC) was different between SelectMDx and PSA (p=0.04) for CS PCa. MLRA showed only SelectMDx test was significantly better for diagnosis of HG and CS PCa with an overall accuracy of 82% ($\beta = 5.57$, $p = 0.001$) and 74% ($\beta = 4.05$, $p = 0.004$), respectively. When PS were added, the overall accuracy of SelectMDx test further improved to 90% ($\beta = 6.38$, $p = 0.001$) and 82% ($\beta = 5.51$, $p = 0.002$), respectively, due to 3 additional men without CS PCa safely avoiding biopsy using SelectMDx ≤ 30% and PS ≤ 3 as cutoffs.

Conclusions: mpMRI has very high sensitivity, but low specificity for HG and CS PCa. SelectMDx test has high specificity to identify men without the respective diseases. mpMRI with SelectMDx test can spare men from unnecessary prostate biopsy.

Source of Funding: The study was supported in parts by the Bingham Research Fund and Schramm Foundation.

Table: SelectMDx, phi, and PIRADS Results Compared to Histopathology of TMB

Performance Measure	SelectMDx > 0%		phi ≥ 27		PIRADS ≥ 3	
	HG PCa	CS PCa	HG PCa	CS PCa	HG PCa	CS PCa
Sensitivity	80%	67%	93%	94%	93%	94%
Specificity	88%	81%	29%	33%	21%	24%
PPV*†	36%	28%	10%	14%	9%	12%
NPV*†	98%	96%	98%	98%	97%	97%
Accuracy	82%	74%	54%	62%	49%	56%
AUC of ROC Curves	0.83	0.75	0.81	0.75	0.72	.066
AUC with PIRADS	0.89	0.8	0.84	0.8	-	-

*PPV = positive predictive values; NPV = negative predictive value
†NPV = and PPV calculated assuming HG cancer prevalence = 8% and CS cancer prevalence = 10%

19-012

Comparison of SelectMDx, Prostate Health Index, and MRI for Diagnosis of High-Grade Prostate Cancer

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Introduction and Objective: High-grade (HG) prostate cancer (PCa) (Gleason Score ≥ 7) has poor clinical prognosis. Thus, clinicians rely on prostate cancer biomarkers and multiparametric magnetic resonance imaging (mpMRI) to screen patients prior to prostate biopsy. We evaluated performance of SelectMDx, prostate health index (PHI), and mpMRI for diagnosis of HG PCa using 5 mm grid interval transperineal mapping biopsy (TMB) shown to have 98% correlation with radical prostatectomy pathology.

Methods: 39 patients with SelectMDx, phi, and mpMRI tests prior to TMB after inconclusive TRUS biopsy results. phi was evaluated using proPSA, free PSA and total PSA in serum. SelectMDx test measured mRNA levels of the HOXC6 and DLX1 in post-DRE urine. phi < 27 indicates men free of PCa and SelectMDx score = 0% correlates with men free of HG PCa. mpMRI was reviewed by a radiologist using Prostate Imaging Reporting and Data System (PIRADS v2) score (PS). PS of 3, 4, and 5 designate intermediate, high, and very high risk of clinically significant (CS) PCa defined as a lesion with HG PCa or volume ≥ 0.5 cc. Histopathology data of TMB was independently read by a genitourinary pathologist. Multivariate logistic regression analyses (MLRA) and receiver operating characteristic (ROC) curves were used to determine diagnostic accuracy. DeLong test was used to determine statistical significance of ROC curves.

Results: The median age was 65 years with mean PSA 6.4 ± 5.9 ng/mL, PSA density (PSAD=PSA/gland volume) 0.16 ± 0.18, and phi 46.5 ± 22.9 at TMB. MB identified 34/39 (87%) patients with PCa and 15/34 (44%) had HG and 18/34 (53%) had CS PCa. Performance results are summarized in the Table. Except between SelectMDx and PSA (p=0.04) for CS PCa, there were no differences in ROC curves of SelectMDx, phi, PIRADS, PSA, PSAD, proPSA, and free PSA for the diagnosis HG or CS PCa. MLRA showed SelectMDx test was significantly better than the rest for diagnosis of HG (β = 5.57, p = 0.001) and CS (β = 4.05, p = 0.004) PCa with an overall accuracy of 82% and 74%, respectively.

Conclusions: SelectMDx is better suited to identify patients with HG or CS PCa prior to prostate biopsy. Patients with negative SelectMDx test results may be spared from prostate biopsy.

Source of Funding: The study was supported in parts by the Bingham Research Fund and Schramm Foundation.

Table: Performance of SelectMDx, phi, and PIRADS Compared to Histopathology of TMB

Performance Measure	SelectMDx > 0%		phi ≥ 27		PIRADS ≥ 3	
	HG Cancer	CS Cancer	HG Cancer	HG Cancer	HG Cancer	HG Cancer
Sensitivity	80%	67%	93%	94%	93%	94%
Specificity	88%	81%	29%	33%	21%	24%
PPV*†	36%	28%	10%	14%	9%	12%
NPV*†	98%	96%	98%	98%	97%	97%
Accuracy	82%	74%	54%	62%	49%	56%
AUC of ROC Curves	0.83	0.75	0.81	0.75	0.72	.066

*PPV = positive predictive values; NPV = negative predictive value; AUC = area under the ROC curve

19-013

Clinical Utility of SelectMDx and Prostate Health Index Tests for Diagnosis of High-Grade Prostate Cancer

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Introduction and Objective: Identifying patients at increased risk of high-grade (Gleason scores ≥ 7) prostate cancer (PCa) before biopsy is a major clinical challenge. Thus, we evaluated the clinical utility of SelectMDx and Prostate Health Index (phi) tests for diagnosis of HG PCa as compared with transperineal mapping biopsy (TMB) results, which is the current diagnostic gold standard. With TMB, an average of 80 prostate needle biopsies are taken every 5 mm for a diagnostic accuracy of 98%.

Methods: 70 patients were selected who had TMB between 2010 and 2018. They were evaluated with both SelectMDx and phi tests from before or after TMB; all had serum and post-digital rectal examination urine samples collected prior to treatment, stored in our biorepository. phi was evaluated using proPSA, free PSA and total PSA in serum. SelectMDx test measured mRNA levels of the HOXC6 and DLX1 in post-DRE urine. Published data shows that phi < 27 indicates patient free of PCa and SelectMDx score = 0% correlates with patient free of HG PCa. Test results were compared against TMB histopathology data. Multivariate logistic regression (MLS) analyses and receiver operating characteristic (ROC) curves were used to determine diagnostic accuracy. DeLong test was used to determine statistical significance of ROC curves. All analyses were done for diagnosis of any PCa and HG PCa.

Results: TMB histopathology showed 17/70 patients with no PCa and 22/53 with HG PCa. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each test are shown in the table below. Pairwise ROC comparison showed no statistically significant difference in the area under the curve of diagnosing PCa (0.75 vs 0.65) and HG PCa (0.71 vs 0.81) by phi and SelectMDx tests respectively. MLS analyses showed phi was significantly better than SelectMDx for diagnosing PCa ($\beta = 0.054$; $p=0.005$) and SelectMDx was significantly better than phi for diagnosing HG PCa ($\beta = 8.45$; $p=0.0002$).

Conclusions: SelectMDx test has high sensitivity and NPV, and therefore, it is more useful than phi for screening patients at risk of high-grade PCa prior to biopsy.

Test	Any PCa (Gleason scores ≥ 6)				High-grade PCa (Gleason scores ≥ 7			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
phi	79%	53%	45%	45%	50%	85%	61%	79%
SelectMDx	45%	77%	86%	31%	**82%**	75%	60%	**90%**

19-014

Clinical Experience with a DNA Specimen Provenance Assay

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Introduction: The diagnostic workup for prostate cancer patients is a complex, multi-step process with the results of each individual core biopsy ultimately impacting the clinician's treatment plan. It is, therefore, critical to ensure the provenance and purity of all core specimens used for diagnosis. Specimen provenance complications (SPCs) have been well documented wherein specimens from two or more patients become completely transposed (Type 1) or admixed among multiple patients (Type 2), often leading to significant diagnostic errors and potentially inappropriate or unnecessary treatment. The Know Error DNA specimen provenance assay (DSPA) uses short tandem repeats in patient DNA to positively identify occult errors prior to delivering treatment. Here, we report our findings over the last 24 months.

Methods: All specimens putatively diagnosed as positive for prostate cancer and received at Strand Diagnostics's laboratory between 10/01/2016 and 09/30/2018 were selected for this analysis. Specimens received from practices that did not order DSPA testing throughout the entire 24 month period were excluded to allow for longitudinal comparison. DSPA results were pulled from a central database and patient and practice information was de-identified to ensure anonymity of results. Type 1 and 2 error rates were calculated across all clients (representing a combination of community, hospital, and academic practices).

Results: During the 24 month review period, 1,316 physicians from 95 practices used the DSPA system for 104,894 patients biopsied for prostate cancer. DSPA was subsequently ordered on 52,610 patients. DSPA testing was completed on 136,594 putatively positive tissue samples (mean = 2.6 cores/patient) and identified 1,059 unique SPC events. The data were analyzed by semi-annual periods to identify trends (Table 1). Overall, 2.0% of biopsy patients were subject to provenance complications (0.17% Type 1 and 1.84% Type 2), an SPC rate which remained stable longitudinally. Importantly, all practices experienced at least one Type 1 or 2 error during the 24 month review period, indicating that no clinical setting is immune to provenance errors despite adoption of best specimen handling practices.

Conclusion: These data confirm that specimen provenance complications persist at a rate of approximately 2% of all putatively positive prostate biopsies, consistent with previously reported rates. This finding is particularly significant given the increased utilization of genetic biomarkers to inform treatment decisions. Genetic testing in the absence of DSPA is subject to the same occult error rate. Use of DSPA testing improves diagnostic accuracy and patient safety, and reduces unnecessary treatment.

Table 1. SPC Rate Across All Practices

Time Period	Type 1 SPCs (%)	Type 2 SPCs (%)	Matches (%)	Total SPCs (%)%
First Half Year (10/01/2016-03/31/2017)	28 (0.24%)	203 (1.75%)	11,376 (98.00%)	237 (1.99%)
Second Half Year (04/01/2017-09/30/2017	25 (0.20%)	240 (1.91%)	12,329 (97.90%)	268 (2.10%)
Third Half Year (10/01/2017-03/31/2018)	22 (0.17%)	235 (1.77%)	12,998 (98.06%)	258 (1.94%)
Fourth Half Year (04/01/2018-09/30/2017)	14 (0.09%)	292 (1.93%)	14,837 (97.98%)	307 (2.02%)
Total (10/01/2016-09/30/2018)	89 (0.17%)	970 (1.84%)	51,540 (97.99%)	1,059 (2.01%)

19-015

Real-World Study of Enzalutamide and Abiraterone Acetate (with Prednisone) Tolerability (REAAcT) – Results

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Background: Enzalutamide (E) and abiraterone acetate with prednisone (AAP) are approved for treatment (tx) of metastatic castration resistant prostate cancer (mCRPC). Concerns regarding differences in CNS manifestations and tolerability between E and AAP have been reported. REAAcT evaluated tolerability in patients (pts) newly starting E and AAP as first line tx for mCRPC.

Methods: This was a multicenter, Phase IV, non-randomized, prospective real-world study (NCT02663193). The tx (E or AAP) determined by the treating physician was prescribed per USPI. PROs (EORTC QLQ 30, FACIT-Fatigue, FACT-Cog), and tests of 4 cognitive domains (Cogstate) were assessed at baseline (BL) and after 2 months (M2) tx and analyzed for evaluable pts who completed BL and M2 assessments with no major protocol deviations. Descriptive statistics were provided. BL Cogstate scores were used to estimate the rate of cognitive impairment defined as >2SD from age-matched normative means of healthy males on >2 tests. Reliable change index (RCI) was calculated. Pts were noted to have clinically meaningful cognitive change with a performance decline of |RCI|>2 on >2 tests.

Results: Of 100 pts treated, 92 pts were evaluable (E= 46 and AAP=46). Median age was 75 years. BL characteristics and median BL scores were similar between arms, with mild cognitive impairment at BL noted in ~20% of pts. Drug discontinuations due to AEs were similar (1 vs. 2 pts), but more dose reductions due to AEs occurred on E vs. AAP (16% vs. 6%). Overall, more AEs were reported on E vs. AAP (52% vs. 36%), but had similar Grade 3/4 AEs (4% E vs. 6% AAP). Unique neuropsychiatric AEs on E included amnesia, cognitive disorders, memory impairment, and confusional state; and on AAP were cerebrovascular accident, presyncope and spinal cord compression. Regarding fatigue, more AEs were noted on E than AAP (26% vs. 8%) and showed a greater worsening in E than AAP (median change -4 vs. 0) by FACIT-Fatigue. This change within E group was statistically significant (mean, 95% CI -4 (-6.61, -1.39). Four pts on E and 1 pt on AAP had clinically meaningful cognitive decline.

Conclusion: While baseline values were similar between arms, after 2 months of tx, differences of fatigue and neurocognition were noted more often with E than AAP.

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